Brain Tumors and Poliomavirus

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Introduction

Primary brain tumors involve the neoplastic processes arising in the Central Nervous System (CNS) structures[4]. These tumors cause significant morbidity and mortality in both adults and children, despite its incidence is lower than in other types of cancer. Polyomaviruses are a family of non-enveloped dsDNA viruses that infect many vertebrate species. Nowadays there is a big controversy about whether polyomavirus may have an important role on brain's tumors' origins. The aim of this project is to determine if there is an association between John Cunningham Virus (JCV), one member of this virus' family, and some types of CNS tumors (Figure 1).

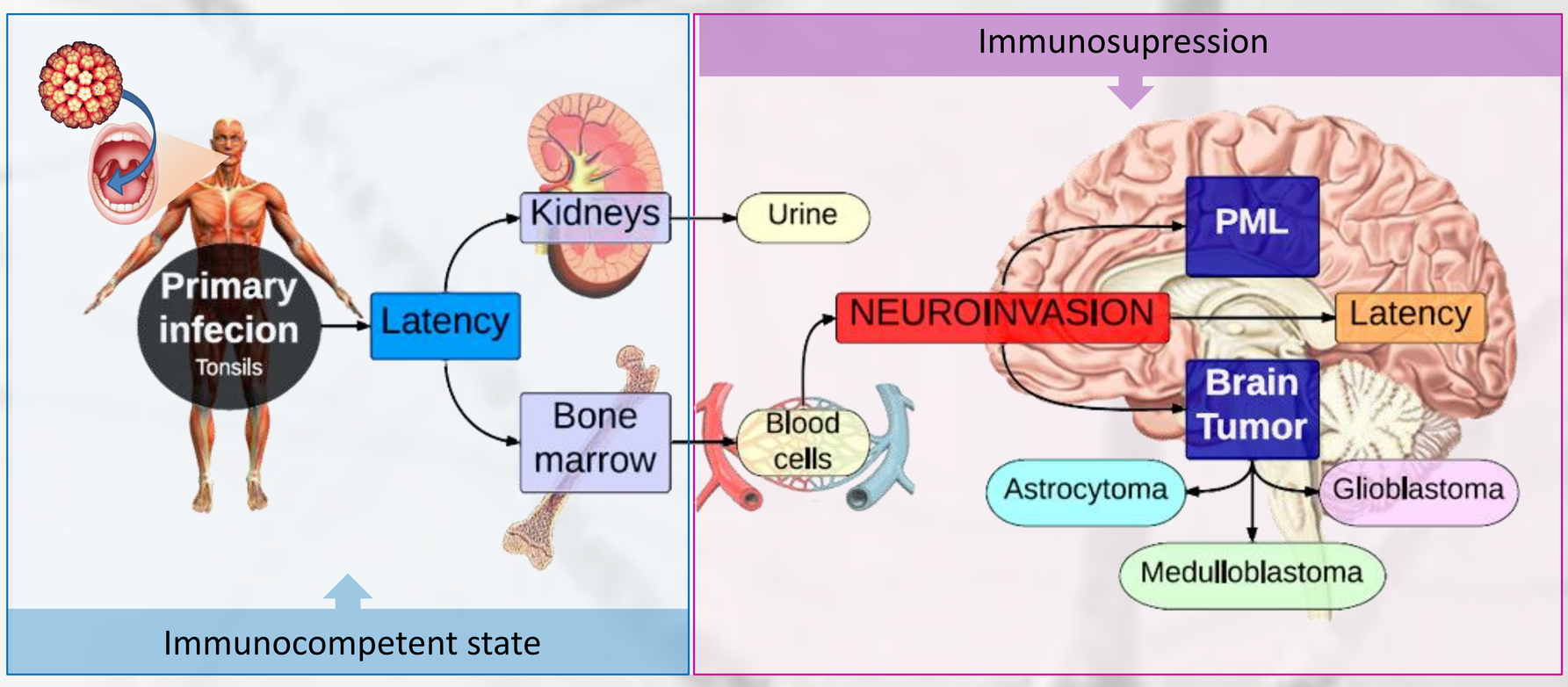
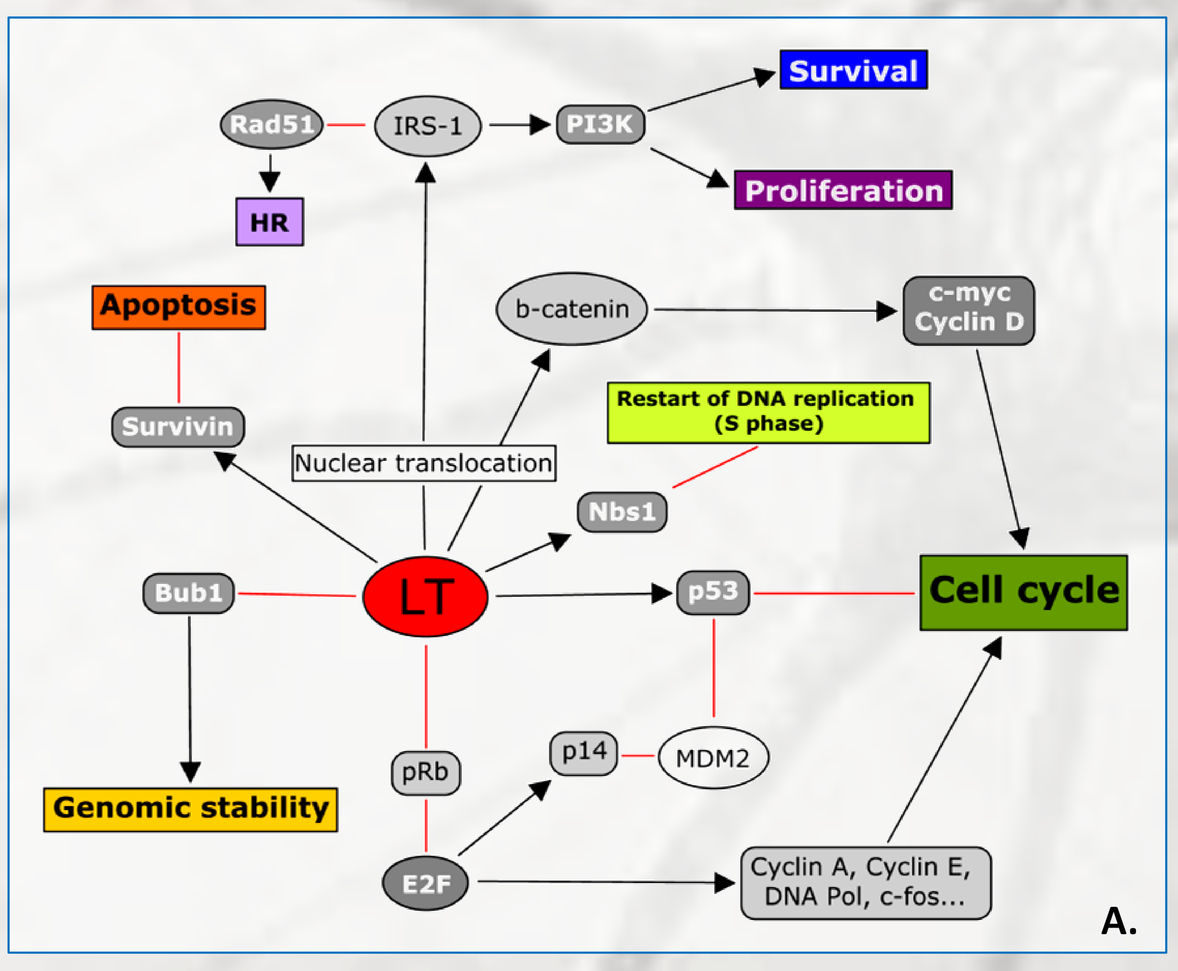
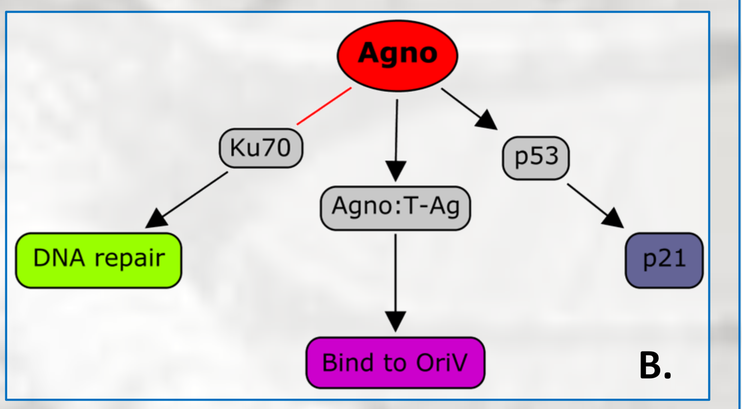


Figure 1. The JCV infection occurs in early ages and is usually asymptomatic. After this primary infection, JCV remains in a latent state. Immunosupressed states can lead to a neuroinvasion. In the brain, JCV can productively infect the oligodendrocytes and conduce to Progressive Multifocal Leucoencephalopaty (PML), a fatal demyelinating disease of the CNS caused by the lysis of this cells. The virus can also remain in the brain in a latent way or induce a tumorigenic process[3]. Astrocytomas, Medulloblastomas and Glioblastomas are the most common brain tumors related with this virus.

Molecular Mechanism involved in tumorigenesis

The most important protein in the tumorigenic process is Large T Antigen (LT) due to its interactions with multiple cellular process (Figure 2A), but other viral proteins are also involved (Figures 2. C-B): small T antigen (st) and Angoprotein (Agno)[1].





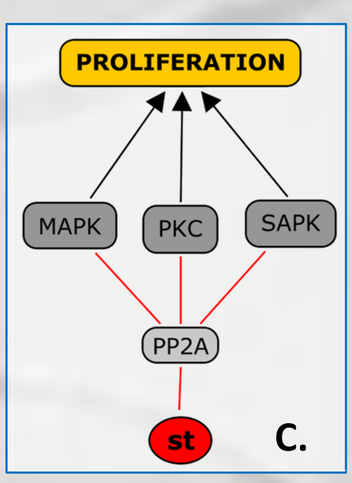


Figure 2. Schema of LT (A), Agno (B) and st (C) interactions with cellular mechanisms.

Possible Association between JCV and Brain Tumors

There are in vivo and ex vivo experiments in favor of the association of JCV and brain tumors:

- Cell cultures have a transformed phenotype after JCV exposure.
- Brain tumors after inoculation of JCV in experimental animals. Brain tumor type depends on the way of administration.
- Transgenics mice for JCV develop tumors in CNS and other types of cancer. The tumoral cells depend on the strand of JCV used.

However, there are not epidemiologic data that supports the correlation between JCV and human neoplasia. JCV is an unique virus and for this reason it is too difficult to develop epidemiologic assays. JCV may influence some cancer types but is not clear in which tumors it is involved. For this reason, the debate remains still open.

Conclusions

High phenotype complexity of cancer makes difficult to determine the specific functions of infectious agents. Moreover, there is a long period of latency between inoculation time and symptom onset and environmental co-factors or host factors modulates the pathogenesis.

Immune system plays a important role in the pathological progression.

Polyomavirus as a risk factor of certain cancers:

JCV could infect the cells in early steps of tumorigenic process. Due to its capacity to induce genomic instability and to interact with cellular proteins, JCV can perform a "Hit and run" mechanism.

It is possible that JCV initially infects rapidly dividing tumor cells and expression of viral early genes then contributes to oncogenesis. If this type of JCV infection occurs in a cell that is already undergoing aberrant cell growth JCV may provide the "2nd hit" according to Knudson's two-hit hypothesis of cancer development.

It's important to develop new therapeutic agents for the possible new aims. There are some effective therapies based on siRNA against LT but it's important to continue the research.

Bibliography

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